Netherlands
The Journal of Medicine

CASE REPORT

Keep an eye out for tubulo-interstitial nephritis

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ABSTRACT

Acute tubulo-interstitial nephritis and uveitis syndrome (TINU) is a rare disease, generally presenting in young women. We describe a 16-year-old Turkish girl with aspecific symptoms and elevated serum creatinine. Further, she complained about a burning pain in her left eye. Renal biopsy revealed acute TIN. Other conditions were excluded and TINU was diagnosed.

KEYWORDS

TINU syndrome, Dobrin syndrome, tubulo-interstitial nephritis, uveitis

What was known on this topic?
TINU is a rare, but treatable, disease generally presenting in young women. The diagnosis is made by exclusion.

What does this add?
Search for deteriorating renal function in patients with uveitis is required, since TIN may be present subclinically. Renal outcome is favourable if treated with corticosteroids. Relapsing uveitis or ocular manifestations can occur after years, thus ophthalmological follow-up is warranted.

INTRODUCTION

Acute tubulo-interstitial nephritis (TIN) is an important cause of acute kidney injury (AKI). Fifteen percent of biopsies for evaluating AKI reveal TIN.[1] The concomitant presentation of TIN and uveitis is an uncommon clinical entity, known as TIN and uveitis syndrome (TINU; also known as the Dobrin syndrome).[2] The diagnosis is of importance, since uveitis can persist or recur for over ten years, whereas renal disease is often self-limiting.[3] However, establishing a diagnosis of TINU may be particularly difficult in some cases, because both manifestations may not occur concurrently. Here, we describe a 16-year-old patient presenting with aspecific symptoms and elevated serum creatinine, in whom a diagnosis of TINU was made.

CASE PRESENTATION

A 16-year-old Turkish woman was admitted to our hospital because of renal impairment. She had been well until three weeks earlier, when her general practitioner prescribed amoxicillin/clavulanic acid because of a urinary tract infection. Thereafter, nausea, vomiting, fatigue, and anorexia developed. The anorexia was associated with a 6 kg weight loss within a two-week period. The patient did not have dysuria, haematuria, a decrease in urine output, or kidney pain. Neither skin lesions nor arthralgia were observed.

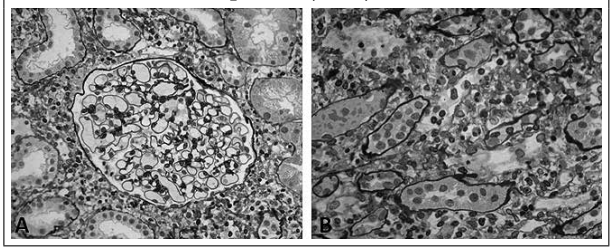
The patient was not critically ill. On examination, no abnormalities were found with the exception of a tender abdomen on palpation. The blood pressure was 117/70 mmHg, pulse 101 beats/min, and temperature 38.1°C. Laboratory tests showed normochromic normocytic anaemia, thrombocytosis, and an increased C-reactive protein (114 mg/l). The white blood cell count revealed no abnormalities. An elevated serum creatinine was found (171 μmol/l, eGFR 34 ml/min). Liver function tests, serum calcium, and protein electrophoresis were normal. Testing for antinuclear antibodies was weakly positive, whereas rheumatoid factor was negative. A urinary screen revealed proteinuria, glycosuria, and erythrocyturia. Microscopic urine analysis showed 2-5 erythrocytes and

10-25 leukocytes per high power field, leukocyte and hyaline casts. Urine and blood cultures were negative.
Ultrasonography excluded postrenal causes, whereas fluid admission did not improve renal function. Testing for antibodies to dsDNA, extractable nuclear antigens, Goodpasture's antigen, anti-neutrophil cytoplasmic antibodies and cryoglobulins was negative. The IgG subclass distribution was normal and complement levels were not reduced.
On the seventh day, she developed a burning pain in her left eye. The ophthalmologist made a diagnosis of non-granulomatous anterior uveitis. The same day, a renal biopsy revealed normal glomeruli, and an infiltrated, oedematous interstitium (*figure 1*). The infiltrate consisted mainly of plasma cells and eosinophils (*figure 1B*). Neither granulomatous lesions nor fibrosis were found. Immunofluorescence was negative. The diagnosis of TINU was made. The patient was treated with systemic and topical corticosteroids. Two weeks after therapy, her renal function and uveitis improved.

DISCUSSION

TINU has been reported in different parts of Europe. However, no cases have been reported in the Netherlands until now. This may be because physicians have been unaware of this syndrome and therefore laboratory evaluations have not been carried out in patients with uveitis and subclinical TIN. Indeed, TINU is a rare disease with a prevalence of 1-2% in tertiary uveitis centres.[4] The classic combination consists of acute TIN and uveitis. As in our case, renal manifestations precede the uveitis in 65% of cases.[5] However, TINU may be underestimated since TIN could be present subclinically in patients with isolated uveitis. Thus, it is of importance to search for systemic symptoms, i.e. fever, weight loss, fatigue, anorexia, and arthralgia. Alongside renal impairment, abnormal liver function tests, anaemia, eosinophilia, and increased erythrocyte sedimentation rate can be found.

Figure 1. *The renal biopsy represents normal glomeruli (A) and an oedematous, (lymphocytic, eosinophilic) infiltrated interstitium (B) suggestive of acute tubulo-interstitial nephritis (TIN)*



Tubular injury can present as a partial or complete Fancony syndrome. TINU is three times more common in women compared with men. Nevertheless, the incidence of the latter is increasing.[6] The mean age is 15 (9-74) years.[5]
The pathogenesis remains poorly understood, but it is thought to be the result of an autoimmune process that might involve cellular and humoral immunity. The former is considered probable since an increased soluble interleukin 2 receptor (sIL2R) level and decreased CD4/CD8 ratio have been described,[7] whereas autoantibodies directed against tubular and ocular antigens have been observed by others.[8,9] Thereby, strong associations with some HLA profiles, i.e. HLA-DRB1*0102,[10] have been reported. The precipitating factor is not known, but infectious as well as non-infectious causes, i.e. medication,[11] are being held responsible for such aberrant immune response.
Combined renal and ocular manifestations are well-known features of some aetiologies. The differential diagnosis must include sarcoidosis, Sjögren syndrome, Behçet's disease, granulomatosis with polyangiitis, systemic lupus erythematosus, rheumatoid arthritis, IgG4-related disease, and infectious diseases, such as tuberculosis. These diseases were excluded by serological testing and histopathological examination. An additive chest X-ray was performed. Neither granulomatous lesions nor bilateral lymphadenopathy were found, excluding sarcoidosis and tuberculosis. According to the diagnostic criteria,[5] a diagnosis of (definite) TINU was made.
In terms of treatment, renal function could improve spontaneously. However, systemic corticosteroid therapy (dose of 1 mg/kg/day for 2-3 weeks) is indicated in the case of progressive renal insufficiency.[12] Relapsing TIN has been described in sporadic cases, in whom a remission was induced by mycophenolate mofetil[13] or cyclosporine A.[14] Since the uveitis is located anteriorly in most cases, local treatment is preferred. Instead of TIN, relapses of the uveitis are not uncommon and seem to be lower in patients treated with systemic corticosteroids.[15] Here, the uveitis responded well to topical and systemic corticosteroid therapy. However, relapses has been described even after ten years.[3] Recurrent ocular manifestations tend to be more severe during relapses. Hence, follow-up with an ophthalmological examination is warranted. Attention must be paid to the development of diffuse vitreous opacities[15] and intraocular complications, i.e. cataract and glaucoma, since complications have been reported in 21% patients with uveitis.[5]

CONCLUSION

TINU is a rare syndrome, generally observed in young women. Male incidence, however, is increasing. In cases of

uveitis, one must search for systemic manifestations and subclinical TIN, since uveitis can present prior to acute TIN. Symptoms respond well to corticosteroid therapy. Nevertheless, ocular manifestations could occur even after long-term follow-up. Hence, ophthalmological follow-up is warranted.

REFERENCES

1. Michel DM, Kelly CJ. Acute interstitial nephritis. J Am Soc Nephrol. 1998;9:506-15.
2. Kaynar K, Ersoz S, Akyol N, et al. Adult onset tubulointerstitial nephritis and uveitis syndrome. Nephrology. 2005;10:418-20.
3. Gafter U, Kalechman Y, Zevin D, et al. Tubulointerstitial nephritis and uveitis: association with suppressed cellular immunity. Nephrol Dial Transplant. 1993;8:821-6.
4. Kump LI, Cervantes-Castaneda RA, Androudi SN, Foster CS. Analysis of pediatric uveitis cases at a tertiary referral center. Ophthalmology. 2005;112:1287-92.
5. Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. Surv Ophthalmol. 2001;46:195-208.
6. Mackensen F, Smith JR, Rosenbaum JT. Enhanced Recognition, Treatment, and Prognosis of Tubulointerstitial Nephritis and Uveitis Syndrome. Ophthalmology. 2007;114:995-9.
7. Yoshioka K, Takemura T, Kanasaki M, Akano N, Maki S. Acute interstitial nephritis and uveitis syndrome: activated immune cell infiltration in the kidney. Pediatr Nephrol. 1991;5:232-4.
8. Abed L, Merouani A, Haddad E, Benoit G, Oligny LL, Sartelet H. Presence of autoantibodies against tubular and uveal cells in a patient with tubulointerstitial nephritis and uveitis (TINU) syndrome. Nephrol Dial Transplant. 2008;23:1452-5.
9. Tan Y, Yu F, Qu Z, et al. Modified C-reactive protein might be a target autoantigen of TINU syndrome. Clin J Am Soc Nephrol. 2011;6:93-100.
10. Mackensen F, David F, Schwenger V, et al. HLA-DRB1*0102 is associated with TINU syndrome and bilateral, sudden-onset anterior uveitis but not with interstitial nephritis alone. Br J Ophthalmol. 2011;95:971-5.
11. Rossert J. Drug-induced acute interstitial nephritis. Kidney Int. 2001;60:804-17.
12. Takemura T, Okada M, Hino S, et al. Course and outcome of tubulointerstitial nephritis and uveitis syndrome. Am J Kidney Dis. 1999;34:1016-21.
13. Hinkle DM, Foster CS. Tubulointerstitial nephritis and uveitis syndrome. Int Ophthalmol Clin. 2008;48:9-13.
14. Gion N, Stavrou P, Foster CS. Immunomodulatory therapy for chronic tubulointerstitial nephritis-associated uveitis. Am J Ophthalmol. 2000;129:764-8.
15. Goda C, Kotake S, Ichiishi A, Namba K, Kitaichi N, Ohno S. Clinical features in tubulointerstitial nephritis and uveitis (TINU) syndrome. Am J Ophthalmol. 2005;140:637-41.